Journal of Autoimmunity 48-49 (2014) 99–103

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg–Strauss syndrome)

Luc Mouthon*, Bertrand Dunogue, Loïc Guillevin

Department of Internal Medicine, National Referral Center for Rare Autoimmune and Systemic Diseases, INSERM U1016, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris, Université Paris Descartes, 27, rue du faubourg Saint-Jacques, 75679 Paris Cedex 14, France

ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 13 October 2013

Keywords:
Eosinophilic granulomatosis with polyangiitis
Churg–Strauss syndrome
Diagnosis criteria
ANCA
Classification

ABSTRACT

Recently, a group of experts in the field suggested to rename Churg–Strauss syndrome as eosinophilic granulomatosis with polyangiitis (EGPA). This condition, first described in 1951, is a rare small- and medium-sized–vessel vasculitis characterized by an almost constant association with asthma and eosinophilia, and, by the presence of anti-myeloperoxidase (MPO) antineutrophil cytoplasm antibodies (ANCA) in 30–38% of the patients. Vasculitis typically develops in a previously asthmatic and eosinophilic middle-aged patient. Asthma is severe, associated with eosinophilia and extrapulmonary symptoms. Most frequently EGPA involves the peripheral nerves and skin. Other organs, however, may be affected and must be screened for vasculitis, especially those associated with a poorer prognosis, such as the heart, kidney and gastrointestinal tract, as assessed by the recently revised Five-Factor Score (FFS). Recent insights, particularly concerning clinical differences associated with ANCA status, showed that EGPA patients might constitute a heterogeneous group. Thus, EGPA patients with anti-MPO ANCA suffered more, albeit not exclusively, from vasculitis symptoms, such as glomerulonephritis, mononeuritis multiplex and alveolar hemorrhage, whereas ANCA-negative patients more frequently develop heart involvement. This observation led to the hypothesis that EGPA might be divided into different clinical and pathophysiological subtypes, which could be managed better with more specifically adapted therapies.

For now, EGPA treatment still relies mainly on corticosteroids and, when necessary for patients with poorer prognoses, combined immunosuppressant drugs, especially cyclophosphamide. Overall survival of EGPA patients is good, despite not uncommon relapses.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly named Churg–Strauss syndrome (CSS), is a rare systemic small- and medium-sized-vessel vasculitis, which distinguishes itself from other small-vessel vasculitides by the presence of severe asthma, and blood and tissue eosinophilia. EGPA was first described in 1951 by Jacob Churg and Lotte Strauss [1] and was initially called allergic angiitis and granulomatosis. Thus, histological findings in these very first patients included necrotizing vasculitis, eosinophilic infiltrates in tissues and granulomas. Since it is rare to identify the three lesions in the same patient, the diagnosis of EGPA mainly relies on clinical parameters. Since then, specific criteria, which are now reliable tools for classifying EGPA among vasculitides [2,3] (Table 1), have been established.

EGPA is most commonly revealed by the onset of vasculitis manifestations – mononeuritis multiplex, purpura and general symptoms – and eosinophilia, in a previously asthmatic patient. However, some patients may develop asthma or eosinophilia simultaneously with vasculitis and sometimes although rarely, in the weeks following its onset [4]. In two recent series, a minority (less than 10%) of patients do not have asthma [5,6]. Another feature of EGPA is its association, among 30–40% of the patients, with antineutrophil cytoplasm antibodies (ANCA) [5–8]. The clinical presentation of these ANCA-positive patients differs significantly from that of ANCA-negative patients, with more frequent mononeuritis multiplex and glomerular nephritis in the former, and more cardiomyopathy in the latter [5,7,8]. This observation led to the hypothesis that EGPA might be divided into different clinical and pathophysiological subtypes, which could be managed better with more specifically adapted therapies.

For now, EGPA treatment still relies mainly on corticosteroids and, when necessary for patients with poorer prognoses [9], combined immunosuppressant drugs, especially cyclophosphamide.

* Corresponding author. Tel.: +33 (0) 1 58 41 20 31; fax: +33 (0) 1 58 41 20 80.
E-mail address: luc.mouthon@cch.aphp.fr (L. Mouthon).

0896-8411/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2014.01.018

Table 1
Churg Strauss syndrome: American College of Rheumatology classification criteria [2].

Asthma
Eosinophilia
History of allergy
Pulmonary infiltrates, non fixed
Paranasal sinus abnormalities
Extravascular eosinophils

4 out of 6 criteria should be present

Overall survival of EGPA patients is good, despite not uncommon relapses.

2. Epidemiology

2.1. Incidence and prevalence

EGPA is a rare disease and one of the less common vasculitides. Its prevalence, in the general population, ranges from 10.7 [10] to 13 [11] cases/million inhabitants, with an annual incidence of 0.5–6.8 new cases/million inhabitants [12–14], depending on their geographical location and the classification criteria applied. Among the asthmatic population, the EGPA incidence is higher, ranging from 34.6 [15] to 64.4 [12] cases/million patient-years. Notably, the incidence of EGPA among asthmatics does not vary, whatever the previous treatments taken, especially concerning their use of leukotriene-receptor antagonists. EGPA may occur at all ages, with a mean age at diagnosis of 48 years [4], without clear sex predominance.

2.2. Triggering factors

EGPA seems to develop following an inflammatory response directed at target antigens. Thus, a number of observations have been reported of patients described as having developed EGPA after being exposed to certain triggering agents. Various environmental agents have been involved, including infectious agents [4], drugs, desensitization or vaccination which could trigger the occurrence of EGPA [7]. Thus, macrolides [16], carbamazepine [17] and quinine [18], and, finally, allergic hyposensitizations and vaccinations [19] have been reported to trigger EGPA. Other triggers have been considered, particularly the use of anti-asthmatic drugs, like the leukotriene-receptor antagonists, montelukast, zafirlukast [20–23], and, more recently, the recombinant anti-IgE monoclonal antibody, omalizumab [24–26]. However, the number of studies supporting these observations is limited, and it might be that incriminated drugs are only indirectly implicated, due to their efficacy that allows to taper the glucocorticoid dose, revealing latent EGPA. It seems that these drugs, as well as other factors might in fact represent only one of a multistep process [27] leading to the occurrence of the disease, and should not lead to preclude to use them if it is absolutely needed. Thus, if some patients developed disease flares after vaccination, this should not preclude us not to vaccine fragile patients, particularly when they are exposed to infections. We have recently conducted a prospective study in patients with systemic inflammatory diseases including EGPA patients and observed that vaccination was well tolerated [28].

The authors of a recent case–crossover study [27] concluded that the montelukast–EGPA link could be drug-related, essentially as a consequence of steroid-tapering, or be purely coincidental, with the drug having been prescribed to treat already present EGPA that had not yet been diagnosed.

3. Clinical features

In addition to the respiratory tract, which is almost constantly involved in EGPA as asthma, any organ system can be affected, either through eosinophil infiltration, granuloma or, most frequently, vasculitis. Once the vasculitic process begins, systemic symptoms appear, often accompanied by organ-associated vasculitic symptoms, like mononeuritis multiplex and necrotic vascular purpura. However, not all EGPA patients have such characteristic disease onset, as clinical manifestations may vary widely. Moreover, once EGPA is suspected, vasculitis involvements of the gut, kidney and/or heart must be sought, because of their proven significant association with poorer prognoses [9]. Herein we will not describe all clinical manifestations of EGPA, which are encountered with various frequencies in the different studies [4,19,29–33], as summarized in Table 2.

4. Complementary investigations

Blood hypereosinophilia, high IgE titers and anti-MPO P-ANCA–positivity are the three main laboratory anomalies found in EGPA. Inflammation is present in 80% of these patients; it is intense and often accompanied by anemia (83%) [4].

Eosinophilia fluctuates during EGPA but is a constant symptom. An eosinophil count exceeding 1500/mm^3 or 10% of the total white blood cell count has been retained as one of the diagnostic criteria for EGPA [29]. Its mean value ranges from 4400 to 8190 [4,7,8], but eosinophils may disappear rapidly after corticosteroids are started.

IgE is elevated at diagnosis in 75% of patients but is non-specific, and is usually not seen in patients taking corticosteroids for their asthma.

ANCA, predominantly P-ANCA of anti-MPO specificity, are present in close to 40% of EGPA patients but some can be anti-proteinase 3 (PR3). ANCA titers do not correlate with disease-evolution characteristics.

Rheumatoid factor-positivity was reported for 22 of the 41 (53.6%) published cases [29]. Antinuclear antibodies are usually absent.

Eosinophil-containing bronchoalveolar lavage fluid is also possible [34]. Renal involvement should be sought by measuring the serum creatinine level and urinalysis, to search for proteinuria and hematuria. Finally, biopsies with histological evidence of granulomas (18%), tissue eosinophilia (52%) and/or necrotizing small-vessel vasculitis (55%) also contribute to diagnosing EGPA [7].

Among imaging techniques, chest X-ray is the first examination to be done. In our experience, it revealed abnormalities in 37.5% of the patients [4] who had bilateral and migratory infiltrates or mixed interstitial patchy alveolar opacities, which can be further evaluated by chest CT scans.

Angiography, when performed, may show typical stenoses consistent with vasculitis in up to one-third of the patients [4], extremely rarely associated with microaneurysms.

Imagery is also important to detect cardiac abnormalities, which must systematically be sought because of their poor prognosis. It should initially consist of an electrocardiogram, chest X-ray, and echocardiogram. Coronary arteriography may be decisive in detecting underlying ischemic cardiopathy, distinct from EGPA cardiomyopathy. Recently, CMRI was shown to perform better at detecting myocardial involvement in EGPA patients [35,36]. After gadolinium injection, T1-weighted cardiac sequences may reveal centromyocardial, subepicardial and/or subendocardial myocardial delayed enhancement.